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10/544,146	05/05/2006	Shyam S. Mohapatra	USF:T193XC1	9945
23557 7590 07/12/2011 SALIWANCHIK, LLOYD & EISENSCHENK A PROFESSIONAL ASSOCIATION PO Box 142950 GAINESVILLE, FL 32614				
EXAMINER SCHNIZER, RICHARD A				
ART UNIT 1635		PAPER NUMBER		
NOTIFICATION DATE 07/12/2011		DELIVERY MODE ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@uspatents.com

Office Action Summary

Application No.

10/544,146

Applicant(s)

MOHAPATRA ET AL.

Examiner

RICHARD SCHNIZER

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 May 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42, 52, 56, 57, 64-67, 69, 72-75, 78-81 and 83 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 42, 52, 56, 57, 64-67, 69, 72-75, 78-81, and 83 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 5/3/2011.

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 5/3/2011.

Claims 59, 71, 77, and 82 were canceled.

Claims 42, 52, 56, 57, 64-67, 69, 72-75, 78-81, and 83 are pending and under consideration.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

This Application claims priority to provisional applications 60/320108 (filed 4/15/2003), and 60/319964 (filed 2/21/2003). All instant claims are directed to a method using "a vector comprising at least one gene suppressing cassette". In view of the specification as filed, e.g. Figures 1B and 1C, this phrase must be interpreted as embracing vectors comprising at least 2 or 3 gene suppressing cassettes. The claims require each cassette to comprise a polynucleotide encoding an siRNA wherein the

siRNA is linked to a promoter. The 60/320108 application does not clearly provide support for vectors comprising more than gene suppressing cassette wherein each cassette comprises a promoter and siRNA. The '108 specification discusses vector construction at paragraph 14. This passage appears to indicate that two oligonucleotides, each encoding a pol III transcription terminator (TTTTT), were separately cloned into separate U6 expression vectors, one as an Apal/XhoI fragment, and the other as an XhoI/EcoRI fragment. There is no clear support for inserting each of two promoter/siRNA cassettes into a single vector. Accordingly, the '108 application does not provide support for the instant claims under 35 USC 12, first paragraph.

All instant claims read on delivery of siRNA expression cassettes to dendritic cells (DC), polynucleotides comprising SEQ ID NOS: 3 or 4, and target sequences common to 4 serotypes of Dengue virus (DV). Instant claim 57 requires a chitosan conjugate. Instant claim 42 is drawn broadly to viral vectors, and instant claim 43 has a specific embodiment limited to an adenoviral vector. Instant claims 72-75, 77-79, 82, and 83 require administration to DC in vivo. The 60/319964 application does not support any of these embodiments. Because all instant claims read on delivery of siRNA expression cassettes to dendritic cells (DC), polynucleotides comprising SEQ ID NOS: 3 or 4, and target genes common to 4 serotypes of Dengue virus (DV), the '964 application is not considered to fully support the claims under 35 USC 112, first paragraph.

Accordingly the effective filing date of the instant claims is considered to be that of PCT/US2004/005566, i.e. 2/23/2004.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 42, 52, 64, 69, 72, 73, 75, 80, and 81 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Iversen et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002).

Iversen taught methods of inhibiting Dengue virus replication in a human by administration of an antisense oligonucleotide directed against the Dengue genome. SEQ ID NO: 27 inhibited replication of four different Dengue serotypes in Vero cells. See abstract and paragraphs 34, 36, 40, 50, 153, 154, 158, 180, Example 3, Figs 5A-D, and claim 16. Iversen taught several routes of delivery including intravenous, subcutaneous, transdermal, and topical to the skin. See paragraph 154.

Raviprakash taught a method of inhibiting expression of DV gene products in mammalian LLCMK/2 cells by microinjection of antisense directed at the 5' end of the portion of the RNA encoding the structural proteins, and the 3' end of the virus genome. Cells were exposed to DV after delivery of antisense. The target regions were 15 bases in length. Two oligonucleotides were directed to the 3' noncoding sequence. See

abstract; paragraph bridging pages 69 and 70; first full paragraph on page 70; Fig. 1 on page 70; page 73, column 2, lines 22-26.

Adelman taught a plasmid vector encoding an inverted repeat siRNA directed against Dengue virus structural gene prM RNA, and its use to inhibit DV infection by administration to mosquito cells in vitro. See abstract.

Yu taught expression cassettes encoding hairpin siRNAs and their use in mammalian cells. See abstract. Yu disclosed the concepts of including the cassettes in nonviral vectors and in and viral vectors. See last paragraph on page 6052.

Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

It was clear to those of ordinary skill in the art at the time of the invention that there was interest in inhibiting DV replication in human cells, particularly in view of the teachings of Iversen and Raviprakash, and that RNA interference represented an alternative to antisense methods of gene suppression. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Iversen by substituting an expression vector encoding an shRNA directed against DV for the antisense oligonucleotide of Iversen. One would have been motivated to do so in order to obtain the advantages disclosed by Tuschl. One of ordinary skill appreciates that shRNAs operate through the same pathway as siRNAs, and would reasonably expect shRNAs to deliver performance superior to that obtained

using antisense in view of the teachings of Tuschl. One would have had a reasonable expectation of success because the technology for expressing shRNAs in mammalian cells was available prior to the time of the invention (see Yu above), and there was no reason to doubt that it would have functioned in vivo in human cells.

It would have been similarly obvious to target a non-coding region in the 3' end of the DV genome because Iversen demonstrated an antisense oligonucleotide directed against a non-coding region in the 3' end (SEQ ID NO: 27) could inhibit replication of all four DV serotypes.

With regard to whether or not the siRNA vector is administered prior to or after DV infection, Iversen taught that treatment could be either prophylactic or post-infection (paragraph 71). In any case, an infected individual will produce infectious virus such that treatment of an infected individual would be considered to result in the treatment of cells that had not yet become infected, but would become infected subsequent to treatment.

Absent evidence to the contrary, delivery to dendritic cells is considered to be inherent in intravenous administration.

Claims 57 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Iversen et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52, 59, 64, 69, 71-73, 75, 77, and 80-82 above, and further in view of Yu et al (US 6852528).

The teachings of Iversen, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

These references do not teach a vector conjugated with chitosan. However, one of ordinary skill appreciates that there is a wide variety of gene delivery techniques which one may employ interchangeably as a matter of design choice. Among these are microinjection (the method used by Raviprakash), lipofection (used by Adelman (2002) and Yu (2002)). Yu ('528) also taught that a variety of methods could be used to deliver nucleic acids to cells including microparticle formation with polycations such as chitosan-based compounds, as well as liposome-mediated transfection and microinjection. See column 22, lines 17-44; column 23, lines 30-47; and column 31, lines 22-38. It would have been obvious to one of ordinary skill in the art to select any of these commonly used transfection techniques, as they were all well recognized in the art as exchangeable alternatives.

Claims 65-67, 74 and 79 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Iversen et al (US 20050096291), Raviprakash et al (J. Virol. 69(1):69-74, 1995), Adelman et al (J. Virol. 76(24): 12925-12933, 2002), Tuschl et al (US 7,056,704), and Yu et al (PNAS 99(9): 6047-6052, 2002) as applied to claims 42, 52, 59, 64, 69, 71-73, 75, 77, and 80-82 above, and further in view of Hope et al (US Patent 6,136,597)

The teachings of Iversen, Raviprakash, Adelman, Tuschl, and Yu (2002) are summarized above. These references can be combined to render obvious methods of inhibiting DV replication in a human by intravenous administration of a vector encoding an shRNA directed against DV RNA.

The cited references did not teach adeno-associated virus vectors.

Hope taught that expression cassettes could be delivered by a variety of viral or non-viral vectors, including plasmid, adeno associated virus, adenoviral, retroviral, lentiviral, polioviral and herpes viral vectors. See column 13, line 16, to column 14, line 23. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. The various vectors described by Hope are all considered to be equivalent platforms for carrying expression cassettes, so it would have been obvious to use any of them to deliver the expression cassette described above. The structural characteristics of the AAV vector of Hope are indistinguishable from those recited in the instant claims, so the functional characteristic of not causing acute inflammation in dendritic cells is considered to be inherent.

Response to Arguments

Applicant's arguments filed 7/19/10 have been fully considered but they are not persuasive.

Applicant argues at pages 7-8 of the response that one of ordinary skill would not have been motivated to target the 3' noncoding region (3'NCR) of DV with an inhibitory oligonucleotide because the prior art predicted that the 3'NCR formed a stem and loop structure. Applicant relies for support on Zhang (2004), of record for the disclosure of secondary structure models of the 3'NCR, and on several references indicating that secondary structure can interfere with RNA interference. This is thought to be due to the fact that secondary structure can restrict access to target sites. Applicant's arguments are unpersuasive for the following reasons. First, while Applicant has provided evidence that those of skill predict that the 3'NCR comprises secondary structure, there is no evidence of record that suggests that the 3' NCR comprises more secondary structure than any other region of the genome. Those of skill in the art appreciate that most long RNAs will exhibit extensive secondary structure. Here, the evidence of record does not suggest that the 3'NCS comprises so much secondary structure as to preclude access of target sites for oligonucleotides. The prior art of record discloses two antisense oligonucleotides complementary to 3'NCS sequences common to all four DV serotypes. Raviprakash (1995) disclosed one that "showed limited efficacy" ("3'-AS", see page 74, left column, first full paragraph). On the other hand, Iversen disclosed one that was effective at inhibiting all four serotypes (SEQ ID NO: 27, paragraph 180 and Fig. 5). Moreover, Raviprakash also disclosed an antisense

oligonucleotide that targeted a 3'NCS sequence common to 3 serotypes which was very effective against DV type 2, which was only serotype tested (page 74, left column, first full paragraph). Thus the prior art of record does not support the position that the 3'NCS comprises sufficient secondary structure to preclude the function of hybridizing oligonucleotides targeted to conserved regions. On the contrary, one of ordinary skill would have been motivated to target the region targeted by Iversen in view of the results obtained which suggest that any secondary structure present was insufficient to inhibit activity.

At pages 8-11 of the response, Applicant reiterates arguments presented previously regarding whether or not the cited references provide a reasonable expectation of success.

Applicant relies on the Subramanya reference to provide evidence that the specific delivery of small interfering RNA (siRNA) to relevant cell types was a hurdle for RNAi therapeutics was, and that development of a method to introduce siRNA into DCs would be an important step toward using RNAi therapeutically to suppress viral replication in Dengue infection. Applicant asserts that the important step of developing a method to introduce Dengue virus-targeted siRNA into DCs to inhibit viral replication was first achieved by the instant inventors, pointing to Examples 8 and 9 of the instant specification which show that adeno associated virus vectors can transduce DCs, and encoded siRNAs can inhibit subsequent DV infection and DV-induced apoptosis in DCs. Applicant further asserts that none of the cited references shows nucleic acid delivery to

DCs, and concludes that the combined references did not provide one of ordinary skill in the art at the time of the invention with a reasonable expectation of success.

With regard to claims 42, 52, 57, 59, 64-67, 69, 71, and 80, Applicant's arguments are unpersuasive because they are based on the issue of the predictability of transfecting DCs, but do not address the predictability of transfecting other DV targets, such as hepatocytes and macrophages. Note that only claims 72 and dependents explicitly require transfection of DCs. None of the other claims requires transfection of DC cells. An et al (Virology 23: 70-77, 1999, of record) provided evidence that DV could infect hepatocytes in vivo and replicate therein (see abstract and discussion). Applicant has presented no evidence or argument that one of ordinary skill at the time of the invention would not have reasonably expected to be able to deliver siRNA to DV-infected hepatocytes in vivo. Applicant has indicated previously that DV infects and replicates in macrophages (Applicant's Remarks filed 10/27/08 at page 5, penultimate sentence of second full paragraph), and this position is supported by Subramanya (see abstract). However, Applicant has presented no evidence or argument that one of skill in the art at the time of the invention could not have accomplished delivery to macrophages in vivo with a reasonable expectation of success using the methods of the combined references.

Applicant's arguments with specific regard to the unpredictable nature of transfecting DCs are also unpersuasive. While, Subramanya indicated that non-selective transfection methods may not work well for primary hematopoietic cells, this does not necessarily mean that one of ordinary skill would not have had a reasonable

expectation of successfully combining the cited references to arrive at the claimed invention. To circumvent the potential problem of non-selective transfection methods not working well for DCs, Subramanya developed a vector that targeted DCs through the use of a peptide shown to bind DCs specifically. This does not mean that those of ordinary skill in the art at the time of the invention believed that DCs could not be transfected in the absence of such a vector. Applicant has presented no clear evidence that one of ordinary skill would have doubted that at least some DCs would have been transfected by the methods of the combined references, and that DV gene expression would have been inhibited in those transfected cells. On the other hand, the prior art showed that DCs could be transfected *in vivo*. Palmowski et al (J. Immunol. 172: 1582-1587, 2004) demonstrated that dendritic cells could be directly transfected *in vivo* by intravenous administration of lentiviral vectors. See also the following references which disclose *in vivo* transfection of DCs: Condon et al (Nature Medicine 2(10): 1122-1128, 1996), Song et al (Proc. Nat. Acad. Sci. USA 94: 1943-1948, 1997), Porgador et al (J. Exp. Med. 188(6): 1075-1082, 1998), Barratt-Boyes (J. Immunol. 164: 2487-2495, 2000), and Larregina et al (Gene Therapy 8: 608-617, 2001).

Applicant asserts that the Raviprakash reference, alone or in combination with the other references, would not have provided one of ordinary skill with a reasonable expectation of success. Applicant asserts that Raviprakash used monkey kidney cells, not dendritic cells, and disclosed that unmodified antisense oligonucleotides were not effective in bringing about significant inhibition of DV. With regard to the cells used by Raviprakash, the Office notes that there is substantial evidence of record that dendritic

cells were known to be transfectable in vivo (see the previous paragraph). Regarding the effectiveness of antisense in inhibiting DV, Fig. 2, panel A on page 71 of Raviprakash shows that unmodified antisense oligonucleotides were ineffective, but standard phosphorothioate oligonucleotides showed greater inhibition, and C-5 propyne-modified antisense oligonucleotides showed very significant inhibition (see panels B-D). These antisense technologies were well known in 1995 when Raviprakash was published, and so it is reasonable to conclude that Tuschl (with an earliest claimed priority date of 12/1/2000) was aware of them when indicating that siRNA inhibition was superior to antisense inhibition. Moreover, there is no reason of record to expect that antisense or siRNA approaches in general would not function in DCs. Accordingly one of ordinary skill would have had a reasonable expectation of improving on the results of Raviprakash when substituting siRNA for antisense, and when delivering to DCs.

Applicant asserts that the oligonucleotide of Raviprakash that target a sequence conserved in all 4 DV serotypes (denoted as "3'a") showed limited efficacy and that in contrast the instant specification exemplified very effective inhibition of DV infection and DV-induced apoptosis in human dendritic cells. This is true, but it does not adequately support Applicant's position that one of ordinary skill would have ignored the 3'NCS as a target for siRNA. Iversen provided objective evidence that a region of the 3'NCS common to all four serotypes was accessible to antisense oligonucleotides, and Raviprakash provided more objective evidence that there at least one other 3'NCS accessible to antisense, i.e. the target site for 3'b-AS. Thus, contrary to Applicant's

statement bridging pages 10 and 11 of the response, there was a reasonable expectation that siRNA directed to the 3'NCS, and to a region therein conserved among the four DV serotypes, would function to inhibit DV replication.

Applicant asserts that at the time the application was filed, "even successful targeting with antisense did not necessarily confer a reasonable expectation of success in those region with siRNA." This is a statement of attorney opinion that is unsupported by evidence. The prior art of record suggests that siRNAs were generally considered to be more active than antisense (see Tuschl above), and this is sufficient to provide a reasonable expectation that siRNA can be successfully substituted for antisense. Absolute predictability is not required to establish a prima facie case of obviousness.

Applicant asserts that the Adelman reference is not relevant to inhibiting DV in human cells or a human. By way of clarification, the Adelman reference is relevant to the rejection because it disclosed the concept of RNA interference inhibition of DV replication, showed that it could function in cells, and disclosed accessible target regions for RNAi.

Applicant asserts that dengue pathogenesis is characterized by overproduction of inflammatory cytokines, including TNF alpha, which is implicated in the vascular leakage that characterizes DHF/DSS, and the plasma levels of which are elevated during acute infection. There it is important to consider whether or not blockade of host molecules such as TNF-alpha also interferes with a possible antiviral effect that might outweigh its pathogenic potential, and relies for support on Subramanya (2010). Applicant asserts that the instant specification shows that interfering RNA did not induce

acute inflammation in human DC as determined by the level of pro-inflammatory cytokines including TNF-alpha.

The Examiner has previously indicated that the relevance of this argument is unclear to him, and that Applicant appears to be arguing limitations that are not in the claims. Applicant responds that, in determining the differences between the cited references and the claims, the invention as a whole must be considered, including those properties that may not be recited in the claims but are inherent in the subject matter and are disclosed in the specification. In response, the Examiner notes that differences between the cited art and inherent features of the claimed invention do not in this case appear to render the claims non-obvious. The cited art accounts for all of the limitations of the claims, and there is motivation to combine the references with a reasonable expectation of success. To the extent that Applicant may be arguing that the invention provides unexpected results, there is no evidence that the results relied on are of statistical significance as required by MPEP 716.02.

The remainder of Applicant's response addresses rejections based on those discussed above, wherein the rejections cite further references. Applicant argues that these further references do not remedy perceived deficiencies in the previous references. These arguments are unpersuasive for the reasons set forth above.

In conclusion, the Office finds that one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of achieving some level of DV inhibition in humans through the combination of the cited references. This is particularly true in view of the fact that antisense had been shown to inhibit DV replication in vitro,

and RNA interference was considered to be superior to antisense for purposes of gene expression inhibition. Iversen suggested delivery of nucleic acids to the skin, and the prior art of record demonstrated that DCs could be transfected by this route. Moreover, it was known that DV could infect hepatocytes in vivo, and that nucleic acids could be delivered to liver cells by intravenous administration. Accordingly one of ordinary skill would have had a reasonable expectation of obtaining some level of DV inhibition through the in vivo administration of siRNAs directed to DV RNA.

For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Heather Calamita, can be reached at (571) 272-2876. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Richard Schnizer/
Primary Examiner, Art Unit 1635